CLAIMS

WE CLAIM:

1. A method for identifying a segregating mutation at a genetic locus that modifies an index phenotype in an index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing a founder inbred strain to an index inbred strain to obtain F_1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, wherein some of the F_1 progeny that carry the dominant allele also carry at least one random mutation;

backcrossing the F_1 progeny to the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least some of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype; and

verifying that the outlying phenotype is caused by a segregating mutation.

2. A method as claimed in Claim 1 wherein any of the crosses employ preserved gametes.

3. A method as claimed in Claim 1 wherein the F_1 progeny and some of the N2 progeny exhibit an extreme outlying phenotype.

4. A method as claimed in Claim 3 wherein the segregating mutation is a heterozygous modifier of the index phenotype selected from a group consisting of an enhancing modifier and a suppressing modifier.

5. A method as claimed in Claim 1 wherein the dominant allele is a *Min* allele at an *Apc* locus.

6. A method as claimed in Claim 1 wherein the index inbred strain is an isogenic index strain that carries single nucleotide polymorphisms.

7. A method as claimed in Claim 6 wherein the isogenic index strain is produced by a method comprising the steps of:

treating an animal of an index strain with a mutagenic agent to induce point mutations in the treated animal;

crossing the treated animal to an animal of the index strain to produce F1 progeny; and

sib-mating F1 and subsequent generation progeny until detrimental and lethal mutations are eliminated.

8. A method as claimed in Claim 1 wherein the founder inbred mouse strain is produced by a method comprising the step of treating a wild-type inbred mouse with a mutagenic agent to induce point mutations.

9. A method as claimed in Claim 8 wherein the mutagenic agent is ethylnitrosourea.

10. A method for identifying a human genetic sequence that corresponds to a segregating mutation at a genetic locus in a non-human animal, the segregating mutation causing an outlying phenotype relative to an index phenotype in an index inbred mouse strain, the method comprising the steps of:

outcrossing a founder inbred non-human strain to an index inbred non-human strain to obtain F_1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, wherein some of the F_1 progeny that carry the dominant allele also carry at least one random mutation;

backcrossing the F_1 progeny to the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least some of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype;

verifying that the outlying phenotype is caused by a segregating mutation;

identifying genetic markers linked to the segregating mutation;

identifying a gene on a contig that encodes the segregating mutation; and

recovering human genetic sequences that correspond to the mutation-encoding gene.

11. A method for identifying a segregating mutation at a genetic locus that modifies an index phenotype in an index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

crossing a founder inbred strain with an index inbred strain to obtain Gen1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, the allele being provided on a genetic background of the wild-type founder inbred strain, wherein some of the Gen1 progeny that carry the dominant allele also exhibit a modified index phenotype; and

verifying that Gen1 progeny that carry the dominant allele and exhibit a modified index phenotype carry a segregating mutation.

12. A method as claimed in Claim 11 wherein the genetic background has no modifying effect upon the index phenotype.

13. A method as claimed in Claim 11 wherein the genetic background has a modifying effect upon the index phenotype.

14. A method as claimed in Claim 13 wherein the genetic background has an enhancing effect upon the index phenotype, and wherein the Gen1 animals exhibit a suppressed phenotype relative to the index inbred strain.

15. A method as claimed in Claim 11 further comprising the steps of:

mapping the segregating mutation by crossing Gen1 animals that have the dominant allele and a modified index phenotype to a genetically distinguishable inbred strain; and

evaluating the progeny of the mapping cross.

16. A method as claimed in Claim 15 wherein the genetically distinguishable inbred strain is an inbred strain having the genetic background of the wild-type founder inbred strain and further comprising single nucleotide polymorphisms relative to the wild-type founder inbred strain.

17. A genetically altered mouse having a genetic background characteristic of a first inbred mouse strain, the mouse comprising in its genome:

a dominant heterozygous allele that confers an index phenotype on a mouse having the characteristic genetic background; and

a segregating modifier of the index phenotype, the modifier being genetically linked to a genetic marker characteristic of a second inbred mouse strain,

wherein the index phenotype in the genetically altered mouse is modified relative to the index phenotype in a mouse that comprises the dominant allele on the genetic background characteristic of the first inbred mouse strain but which lacks the segregating modifier.

18. A mouse as claimed in Claim 17 wherein the dominant allele is a *Min* allele at an Apc locus.

19. A non-human animal comprising a segregating mutation that modifies an index phenotype, the animal being prepared according to a method comprising the steps of:

outcrossing a founder inbred non-human strain to an index inbred non-human strain to obtain F_1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, wherein some of the F_1 progeny that carry the dominant allele also carry at least one random mutation;

backcrossing the F_1 progeny to the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least some of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype;

verifying that the outlying phenotype is caused by a segregating mutation; and

selecting an animal that shows the outlying phenotype.

20. A non-human animal as claimed in Claim 19 wherein the non-human animal is a mouse.

21. A non-human animal comprising a segregating mutation that modifies an index phenotype, the animal being prepared according to a method comprising the steps of:

crossing a founder inbred strain with an index inbred strain to obtain Gen1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, the allele being provided on a genetic background of the wild-type founder inbred strain, wherein some of the Gen1 progeny that carry the dominant allele also exhibit a modified index phenotype;

verifying that Gen1 progeny that carry the dominant allele and exhibit a modified index phenotype carry a segregating mutation; and

selecting an animal that shows the outlying phenotype.

22. A non-human animal as claimed in Claim 21 wherein the non-human animal is a mouse.

23. A non-human animal comprising a segregating mutation that modifies an index phenotype, the animal being prepared according to a method comprising the steps of:

outcrossing a founder isogenic inbred strain with the index inbred strain to obtain Gen1F_1 progeny, the founder isogenic strain being heterozygous only for random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, where at least some of the Gen1F_1 progeny carry both the dominant allele and at least one random mutation;

crossing a founder animal of the founder isogenic inbred strain to an animal of the founder strain that lacks the mutations to obtain inbred Gen2 offspring, where the founder animal has at least one outcrossed F_1 progeny that displays the outlying phenotype relative to the index phenotype;

outcrossing Gen2 offspring to the index strain to obtain Gen2F_1 backcross progeny, half of which, on average, carry the dominant allele that confers the index phenotype; and

verifying that a subset of the Gen2F_1 progeny shows the outlying phenotype; and

selecting an animal that shows the outlying phenotype.

24. A non-human animal as claimed in Claim 23 wherein the non-human animal is a mouse.

25. A method for identifying a segregating mutation at a genetic locus that modifies an index phenotype in an index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing a founder isogenic inbred strain with the index inbred strain to obtain Gen1F_1 progeny, the founder isogenic strain being heterozygous only for random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, where at least some of the Gen1F_1 progeny carry both the dominant allele and at least one random mutation;

crossing a founder animal of the founder isogenic inbred strain to an animal of the founder strain that lacks the mutations to obtain inbred Gen2 offspring, where the founder animal has at least one outcrossed F_1 progeny that displays the outlying phenotype relative to the index phenotype;

outcrossing Gen2 offspring to the index strain to obtain Gen2F_1 backcross progeny, half of which, on average, carry the dominant allele that confers the index phenotype; and

verifying that a subset of the Gen2F_1 progeny shows the outlying phenotype.

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